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2 page(s) will be printed.

Record: 7

**Title:** Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk.

**Author(s):** Illett KF; Hackett LP; Dusci LJ; Roberts MJ; Kristensen JH; Paech M; Groves A; Yapp P

**Author's Address:** Department of Pharmacology, University of Western Australia, Nedlands.

**Source:** British journal of clinical pharmacology [Br J Clin Pharmacol] 1998 May; 45 (5), pp. 459-62.

**Pub. Type:** Clinical Trial; Journal Article

**Language:** English

**Journal Info:** Country of Publication: ENGLAND NLM ID: 7503323 ISSN: 0306-5251

Citation Subsets: IM

**MeSH Heading:** Breast Feeding\*

Antidepressive Agents/\*pharmacokinetics

Cyclohexanols/\*pharmacokinetics

Milk, Human/\*chemistry

Adult. Antidepressive Agents/analysis. Area Under Curve.

Chromatography, High Pressure Liquid. Cyclohexanols/analysis. Female.

Human. Infant. Infant, Newborn. Milk, Human/metabolism. Support,

Non-U.S. Gov't. Tissue Distribution.

**Abstract:** AIMS: To characterise the transfer of venlafaxine (V) and its O-desmethyl metabolite (ODV) into human milk by measuring milk/plasma (M/P) ratio, and to estimate the likely dose received by a breast-fed infant.

METHODS: Milk and plasma samples were collected from three lactating women who were taking venlafaxine for depression, and were at steady-state. In two of the patients, venous blood and milk samples were collected 0, 1, 2, 3, 4, 6, 8 and 12 h post dose, while in the third patient a single pair of blood and milk samples was obtained 0.83 h post dose. A plasma sample was obtained from each of their infants. V and ODV were measured in plasma and milk by high performance liquid chromatography. M/P was calculated and infant dose estimated as drug concentration in milk x a milk intake of 0.15 l kg(-1) day(-1), relative to the weight-adjusted maternal dose. RESULTS: Mean M/P for V was 4.1 (range 2.8-4.8) and 3.1 for ODV (range 2.8-3.8). The mean total infant dose (as V equivalents) was 7.6% (range 4.7-9.2%) of the maternal weight-adjusted dose, with approximately equal amounts of V (3.5%) and ODV (4.1%) in the dose. ODV (median 100 microg l(-1)) was detected in the plasma of all three infants. The infants were healthy and showed no acute adverse effects. CONCLUSIONS: These preliminary data show that the total dose of V and ODV ingested by breast-fed infants can be as high as 9.2% of maternal intake. Moreover there were measurable concentrations of ODV in the infants' plasma. We recommend that exposed infants should be observed closely.

**CAS Registry No.:** 0 (Antidepressive Agents)  
0 (Cyclohexanols)  
93413-62-8 (O-desmethylvenlafaxine)  
93413-69-5 (venlafaxine)

**Revision Date:** 20001218

**Entry Date(s):** *Date Created:* 19980901 *Date Completed:* 19980901

**Citation ID(s):** *PMID:* 9643618 *Medline UI:* 98305771

**Database:** MEDLINE

**Back**

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=> d his

(FILE 'HOME' ENTERED AT 07:09:05 ON 30 JUN 2002)

FILE 'REGISTRY' ENTERED AT 07:09:24 ON 30 JUN 2002  
E O-DESMETHYLVENLAFAXINE/CN

L1 1 S E3

FILE 'CAPLUS' ENTERED AT 07:10:10 ON 30 JUN 2002

L2 59 S L1

L3 67081 S DEPRESSION OR HYPERACTIVITY OR ATTENTION DEFICIT  
L4 11 S L3 AND L2

=> d bib abs kwic 1-11

L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2002 ACS

AN 2002:310162 CAPLUS

DN 136:395834

TI Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: A preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects

AU Kennedy, Sidney H.; McCann, Sonia M.; Masellis, Mario; McIntyre, Roger S.; Raskin, Joel; McKay, Gordon; Baker, Glen B.

CS Centre for Addiction and Mental Health, and the Department of Psychiatry, University of Toronto, Toronto, ON, Can.

SO Journal of Clinical Psychiatry (2002), 63(3), 181-186  
CODEN: JCLPDE; ISSN: 0160-6689

PB Physicians Postgraduate Press, Inc.

DT Journal

LA English

AB This study was designed to evaluate the effect of combining bupropion sustained release (SR) with venlafaxine, paroxetine, or fluoxetine in patients who reported unacceptable sexual dysfunction when treated with monotherapy with the latter 3 agents. Following a min. of 6 wk of antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI) or venlafaxine (a serotonin-norepinephrine reuptake inhibitor), eligible subjects received a further 8 wk of monitored combination therapy with bupropion SR at a dose of 150 mg/day with no alterations to index antidepressant dosing. There was a clin. significant benefit in 14 (78%) of 18 partial responders or nonresponders, and 33% (N = 6) achieved a full response ( $\chi^2 = 8.06$ , df = 2, p = .017). Sexual dysfunction, particularly a decrease in orgasmic delay, was also significantly improved with combination therapy (men: paired t = -2.1, df = 6, p = .08; women: paired t = -3.0, df = 7, p = .02). Plasma monitoring of drugs and their metabolites revealed a statistically significant increase in venlafaxine levels ( $F = 6.89$ , df = 4,24; p = .001) accompanied by a decrease in O-desmethyl-venlafaxine ( $F = 14.26$ ; df = 4,24; p < .0005) during combined treatment with bupropion SR. There were no statistically significant changes in plasma levels of SSRIs (paroxetine and fluoxetine) during the trial. Bupropion had an effect on the pharmacokinetics of venlafaxine but not those of the SSRIs. Further investigation of combination treatments under randomized, double-blind conditions is recommended.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST antidepressant bupropion venlafaxine paroxetine fluoxetine  
depression anorgasmia sexual dysfunction; bupropion SR venlafaxine  
metabolite desmethylvenlafaxine pharmacokinetic drug interaction  
depression

IT Mental disorder  
(depression, major; bupropion SR with venlafaxine,  
paroxetine, or fluoxetine in sexual dysfunction patients with previous  
monotherapy treatment)

CAPLUS ONLINE PRINTOUT

IT 54910-89-3, Fluoxetine 61869-08-7, Paroxetine 93413-62-8,  
O-Desmethylvenlafaxine 93413-69-5, Venlafaxine  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(bupropion SR with venlafaxine, paroxetine, or fluoxetine in sexual dysfunction patients with previous monotherapy treatment)

L4 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2002 ACS  
AN 2002:111809 CAPLUS

DN 136:288525

TI Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants

AU Ilett, Kenneth F.; Kristensen, Judith H.; Hackett, L. Peter; Paech, Michael; Kohan, Rolland; Rampono, Jonathan

CS Department of Pharmacology, University of Western Australia, Nedlands, 6009, Australia

SO British Journal of Clinical Pharmacology (2002), 53(1), 17-22  
CODEN: BCPHBM; ISSN: 0306-5251

PB Blackwell Science Ltd.

DT Journal

LA English

AB Aims: To characterize milk/plasma (M/P) ratio and infant dose, for venlafaxine (V) and its O-desmethyl metabolite (ODV), in breastfeeding women taking venlafaxine for the treatment of depression, and to det. the plasma concn. and effects of these drugs in their infants.

Methods: Six women (mean age 34.5 yr, mean wt. 84.3 kg) taking venlafaxine (median dose 244 mg day-1, range 225-300 mg day-1) and their seven infants (mean age 7.0 mo, mean wt. 7.3 kg) were studied. V and ODV in plasma and milk were measured by high-performance liq. chromatog. over a 12 h dose interval at steady-state. Infant exposure was estd. as the product of estd. milk prodn. rate (0.15 l kg-1 day-1) and av. drug concn. in milk, normalized to body wt. and expressed as a percentage of the wt.-adjusted maternal dose. Results: Mean M/PAUC values of 2.5 (range 2.0-3.2) and 2.7 (range 2.3-3.2) were calcd. for V and ODV, resp. The mean max. concns. (95% CI) of V and ODV in milk were 1161 (95% CI, 588, 1734) .mu.g l-1 and 796 (362, 1230) .mu.g l-1. Mean infant exposure was 3.2% (1.7, 4.7%) for V and 3.2% (1.9, 4.9%) for ODV (as V equiv.). V was detected in the plasma of one out of seven infants studied (5 .mu.g l-1), while ODV was detected in four of the infants, at concns. ranging from 3 to 38 .mu.g l-1. All of the infants in the study were healthy, as reported by their mothers and/or by clin. examn. on the study day. Conclusions: The concns. of V and ODV in breast milk were 2.5 and 2.7 times those in maternal plasma. The mean total drug exposure (as venlafaxine equiv.) of the breastfed infants was 6.4% (5.5-7.3%), which is below the 10% notional level of concern. There were no adverse effects in any of the infants. The data support the use of V in breastfeeding. Nevertheless, since low concns. of ODV were detected in the plasma of four out of the seven infants studied, we recommend breastfed infants should be monitored closely. Each decision to breast feed should be made as an individual risk:benefit anal.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Aims: To characterize milk/plasma (M/P) ratio and infant dose, for venlafaxine (V) and its O-desmethyl metabolite (ODV), in breastfeeding women taking venlafaxine for the treatment of depression, and to det. the plasma concn. and effects of these drugs in their infants.

Methods: Six women (mean age 34.5 yr, mean wt. 84.3 kg) taking venlafaxine (median dose 244 mg day-1, range 225-300 mg day-1) and their seven infants (mean age 7.0 mo, mean wt. 7.3 kg) were studied. V and ODV in plasma and milk were measured by high-performance liq. chromatog. over a 12 h dose interval at steady-state. Infant exposure was estd. as the product of

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estd. milk prodn. rate (0.15 l kg<sup>-1</sup> day<sup>-1</sup>) and av. drug concn. in milk, normalized to body wt. and expressed as a percentage of the wt.-adjusted maternal dose. Results: Mean M/PAUC values of 2.5 (range 2.0-3.2) and 2.7 (range 2.3-3.2) were calcd. for V and ODV, resp. The mean max. concns. (95% CI) of V and ODV in milk were 1161 (95% CI, 588, 1734) .mu.g l<sup>-1</sup> and 796 (362, 1230) .mu.g l<sup>-1</sup>. Mean infant exposure was 3.2% (1.7, 4.7%) for V and 3.2% (1.9, 4.9%) for ODV (as V equiv.). V was detected in the plasma of one out of seven infants studied (5 .mu.g l<sup>-1</sup>), while ODV was detected in four of the infants, at concns. ranging from 3 to 38 .mu.g l<sup>-1</sup>. All of the infants in the study were healthy, as reported by their mothers and/or by clin. examn. on the study day. Conclusions: The concns. of V and ODV in breast milk were 2.5 and 2.7 times those in maternal plasma. The mean total drug exposure (as venlafaxine equiv.) of the breastfed infants was 6.4% (5.5-7.3%), which is below the 10% notional level of concern. There were no adverse effects in any of the infants. The data support the use of V in breastfeeding. Nevertheless, since low concns. of ODV were detected in the plasma of four out of the seven infants studied, we recommend breastfed infants should be monitored closely. Each decision to breast feed should be made as an individual risk:benefit anal.

ST antidepressant venlafaxine metabolite desmethylvenlafaxine depression pharmacokinetics bioavailability; efexor extended release antidepressant pharmacokinetics human milk infant

IT Mental disorder (depression; venlafaxine (Efexor) and metabolite O-desmethylvenlafaxine distribution in human milk and effect in breastfed infants)

IT 93413-62-8, O-Desmethylvenlafaxine 93413-69-5, Venlafaxine  
99300-78-4, Efexor  
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(venlafaxine (Efexor) and metabolite O-desmethylvenlafaxine distribution in human milk and effect in breastfed infants)

L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2002 ACS  
AN 2001:389518 CAPLUS  
DN 135:282600  
TI Use of vancomycin silica stationary phase in packed capillary electrochromatography. II. Enantiomer separation of venlafaxine and O-desmethylvenlafaxine in human plasma  
AU Fanali, S.; Rudaz, S.; Veuthey, J.-L.; Desiderio, C.  
CS Area della Ricerca di Roma, Consiglio Nazionale delle Ricerche, Istituto di Cromatografia, Rome, Monterotondo Scalo, 00016, Italy  
SO Journal of Chromatography, A (2001), 919(1), 195-203  
CODEN: JCRAEY; ISSN: 0021-9673  
PB Elsevier Science B.V.  
DT Journal  
LA English  
AB A capillary electrochromatog. method, using vancomycin chiral stationary phase packed capillary, was optimized for the simultaneous chiral sepn. of the antidepressant drug venlafaxine and its main active metabolite O-desmethylvenlafaxine. Simultaneous baseline enantiomeric sepn. of the two compds. was obtained using a mobile phase composed of 100 mM ammonium acetate buffer pH 6/water/acetonitrile (5:5:90, vol./vol.). The electrokinetic injection for sample introduction provided a limit of quantitation for both the compds. of 0.05 .mu.g/mL racemate concn. suitable for the anal. of venlafaxine and metabolite in biol. samples. The acetonitrile mobile phase concn. was found to modulate the analytes elution times, the enantiomeric resoln. and the efficiency of the sepn. The column was tested for repeatability and linearity showing RSD values (%) in the range of 0.13-0.24, 2.47-3.66 and 1.35-2.50 for migration time,

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sample/internal std. peak area ratio and enantiomeric resoln., resp. and correlation coeffs. higher than 0.9990. The method was applied to the anal. of clin. samples of patients under **depression** therapy showing a stereoselective metab. for venlafaxine.

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A capillary electrochromatog. method, using vancomycin chiral stationary phase packed capillary, was optimized for the simultaneous chiral sepn. of the antidepressant drug venlafaxine and its main active metabolite O-desmethylvenlafaxine. Simultaneous baseline enantiomeric sepn. of the two compds. was obtained using a mobile phase composed of 100 mM ammonium acetate buffer pH 6/water/acetonitrile (5:5:90, vol./vol.). The electrokinetic injection for sample introduction provided a limit of quantitation for both the compds. of 0.05 .mu.g/mL racemate concn. suitable for the anal. of venlafaxine and metabolite in biol. samples. The acetonitrile mobile phase concn. was found to modulate the analytes elution times, the enantiomeric resoln. and the efficiency of the sepn. The column was tested for repeatability and linearity showing RSD values (%) in the range of 0.13-0.24, 2.47-3.66 and 1.35-2.50 for migration time, sample/internal std. peak area ratio and enantiomeric resoln., resp. and correlation coeffs. higher than 0.9990. The method was applied to the anal. of clin. samples of patients under **depression** therapy showing a stereoselective metab. for venlafaxine.

IT 93413-62-8, O-Desmethylvenlafaxine  
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)  
(use of vancomycin silica stationary phase in packed capillary electrochromatog. for enantiomer sepn. of venlafaxine and O-desmethylvenlafaxine in human plasma)

L4 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2002 ACS  
AN 2000:708682 CAPLUS

DN 134:247114

TI Lithium augmentation of venlafaxine: An open-label trial

AU Hoencamp, Erik; Haffmans, P. M. Judith; Dijken, Wim A.; Huijbrechts, Irma P. A. M.

CS Parnassia, Psycho-Medical Centre, The Hague, Neth.

SO Journal of Clinical Psychopharmacology (2000), 20(5), 538-543

CODEN: JCPYDR; ISSN: 0271-0749

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB The authors conducted an open-label study of the efficacy and tolerability of venlafaxine and of lithium augmentation in outpatients with **depression** who were not responding to venlafaxine. Outpatients aged 18 to 70 yr were eligible if they had a min. baseline score of 16 on the 17-item Hamilton Rating Scale for **Depression** (HAM-D). Patients were started on venlafaxine 37.5 mg twice daily for 1 wk. For weeks 2 through 4, the dose of venlafaxine was increased to 75 mg twice daily, and for weeks 5 through 7, the dose was further increased to 75 mg three times daily. At the end of the 7-wk treatment period, patients with a <50% decrease in their HAM-D scores from baseline were given lithium carbonate 600 mg once daily. The dose of lithium carbonate was adjusted to maintain plasma levels in the range of 0.6 to 1.0 mmol/mL. Efficacy was assessed with the 17-item HAM-D, Montgomery-Asberg **Depression** Rating Scale, and the Clin. Global Impressions Scale. Data were analyzed on an intent-to-treat basis. At the end of the 7-wk treatment period, 35% of patients showed a .gtoreq.50% decrease in their HAM-D scores from baseline. Lithium augmentation was initiated in 23 patients. The results showed that the addn. of lithium was well-tolerated and led to a further decrease in the HAM-D scores, with eight patients responding and two of

## CAPLUS ONLINE PRINTOUT

them presenting a remission. The addn. of lithium to venlafaxine was found to be a well-tolerated strategy in treatment-resistant patients.

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The authors conducted an open-label study of the efficacy and tolerability of venlafaxine and of lithium augmentation in outpatients with depression who were not responding to venlafaxine. Outpatients aged 18 to 70 yr were eligible if they had a min. baseline score of 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D). Patients were started on venlafaxine 37.5 mg twice daily for 1 wk. For weeks 2 through 4, the dose of venlafaxine was increased to 75 mg twice daily, and for weeks 5 through 7, the dose was further increased to 75 mg three times daily. At the end of the 7-wk treatment period, patients with a <50% decrease in their HAM-D scores from baseline were given lithium carbonate 600 mg once daily. The dose of lithium carbonate was adjusted to maintain plasma levels in the range of 0.6 to 1.0 mmol/mL. Efficacy was assessed with the 17-item HAM-D, Montgomery-Asberg Depression Rating Scale, and the Clin. Global Impressions Scale. Data were analyzed on an intent-to-treat basis. At the end of the 7-wk treatment period, 35% of patients showed a ≥50% decrease in their HAM-D scores from baseline. Lithium augmentation was initiated in 23 patients. The results showed that the addn. of lithium was well-tolerated and led to a further decrease in the HAM-D scores, with eight patients responding and two of them presenting a remission. The addn. of lithium to venlafaxine was found to be a well-tolerated strategy in treatment-resistant patients.

IT Antidepressants  
Drug resistance

(lithium augmentation of venlafaxine for treatment of depression in humans)

IT 7439-93-2, Lithium, biological studies 93413-69-5, Venlafaxine

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(lithium augmentation of venlafaxine for treatment of depression in humans)

IT 93413-62-8, O-Desmethylvenlafaxine

RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)

(lithium augmentation of venlafaxine for treatment of depression in humans)

L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2002 ACS  
AN 2000:384124 CAPLUS

DN 133:17270

TI Preparation of (-)-venlafaxine and derivatives as neuronal monoamine reuptake inhibitors.

IN Jerussi, Thomas P.; Senanayake, Chrisantha H.

PA Sepracor Inc., USA

SO PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000032556	A1	20000608	WO 1999-US28303	19991201
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SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG,  
 KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,  
 DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,  
 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 US 6342533 B1 20020129 US 1999-450690 19991130  
 EP 1135359 A1 20010926 EP 1999-968056 19991201  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO  
 PRAI US 1998-110488P P 19981201  
 US 1999-450690 A 19991130  
 WO 1999-US28303 W 19991201  
 AB A pharmaceutical compn. comprising (-)-venlafaxine deriv. substantially free of (+)-stereoisomer is claimed. Thus, (.+-.)-venlafaxine in THF was added to a mixt. prep'd. from Ph2PH and BuLi in THF at 0.degree. followed by stirring and overnight reflux to give 73.8% (.+-.)-O-desmethylvenlafaxine, which was resolved using di-p-toluoyl-L-tartaric acid to give (-)-O-desmethylvenlafaxine. Drug formulations contg. the latter are given.  
 RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT  
 IT Mental disorder  
 (attention deficit disorder, treatment; prepn. of (-)-venlafaxine and derivs. as neuronal monoamine reuptake inhibitors)  
 IT 93413-62-8P 93413-69-5P 93413-76-4P 93413-77-5P  
 93413-90-2P 99300-78-4P 130198-05-9P 149289-29-2P 149289-30-5P  
 272788-00-8P 272788-02-0P 272788-07-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. of (-)-venlafaxine and derivs. as neuronal monoamine reuptake inhibitors)  
 L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2002 ACS  
 AN 2000:384122 CAPLUS  
 DN 133:30575  
 TI Preparation of derivatives of (+)-venlafaxine as inhibitors of neuronal monoamine reuptake.  
 IN Jerussi, Thomas P.; Senannayake, Chrisantha H.  
 PA Sepracor Inc., USA  
 SO PCT Int. Appl., 47 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1  

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000032555	A1	20000608	WO 1999-US28306	19991201
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	US 6197828	B1	20010306	US 1999-450691	19991130
	EP 1135358	A1	20010926	EP 1999-965065	19991201
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, FI			
PRAI	US 1998-110486P	P	19981201		
	US 1999-450691	A	19991130		

CAPLUS ONLINE PRINTOUT

WO 1999-US28306 W 19991201

AB A method of treating an affective disorder comprises administration of a (+)-venlafaxine deriv. substantially free of the (-)-enantiomer. Thus, (.-+.)-venlafaxine (prepn. given) was added to a 0.degree. mixt. of Ph2PH and BuLi followed by stirring and reflux overnight to give 73.8% (.-+.)-O-desmethylvenlafaxine, which was resolved to give (+)-O-desmethylvenlafaxine. Drug formulations contg. the latter are given.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Mental disorder

(attention deficit disorder, treatment; prepn. of derivs. of (+)-venlafaxine as inhibitors of neuronal monoamine reuptake)

IT 93413-62-8P 93413-69-5P, (.-+.)-Venlafaxine 93413-76-4P  
93413-77-5P 93413-90-2P 99300-78-4P 130198-05-9P 149289-29-2P  
149289-30-5P 272788-00-8P 272788-02-0P 272788-07-5P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. of derivs. of (+)-venlafaxine as inhibitors of neuronal monoamine reuptake)

L4 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2002 ACS

AN 2000:279486 CAPLUS

DN 132:288295

TI Venlafaxine serum levels and CYP2D6 genotype

AU Veefkind, Adrian H.; Haffmans, P. M. Judith; Hoencamp, Erik

CS Zon and Schild Psychiatric Center, Amersfoort, 3800 DB, Neth.

SO Therapeutic Drug Monitoring (2000), 22(2), 202-208

CODEN: TDMODV; ISSN: 0163-4356

PB Lippincott Williams & Wilkins

DT Journal

LA English

AB Thirty-three patients with depression treated with 225 mg venlafaxine were genotyped for the polymorphic enzyme, debrisoquine 4-hydroxylase (CYP2D6). The relationship between drug and metabolite levels and between genotype and clin. response were investigated. Although the no. of responders in this study is insufficient for definite conclusions to be drawn, a target therapeutic concn. ranging from 195-400 .mu.g/L for the sum of venlafaxine and O-desmethylvenlafaxine is suggested. The ratio of O-desmethylvenlafaxine to venlafaxine in the serum concns. is a measure of metabolic turnover, and can be used to distinguish between ultrarapid and poor metabolizers. All but one of the nonresponders in this study had lower ratios than the responders. Three patients (9%) had homozygous defective CYP2D6 alleles and did not readily metabolize venlafaxine to O-desmethylvenlafaxine, pointing to poor metab. In these patients, N-desmethylation was increased. Two out of four patients detected by the ratio as potentially ultrarapid metabolizers were shown to have multiple copies of a functional CYP2D6 gene.

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Thirty-three patients with depression treated with 225 mg venlafaxine were genotyped for the polymorphic enzyme, debrisoquine 4-hydroxylase (CYP2D6). The relationship between drug and metabolite levels and between genotype and clin. response were investigated. Although the no. of responders in this study is insufficient for definite conclusions to be drawn, a target therapeutic concn. ranging from 195-400 .mu.g/L for the sum of venlafaxine and O-desmethylvenlafaxine is suggested. The ratio of O-desmethylvenlafaxine to venlafaxine in the serum concns. is a measure of metabolic turnover, and can be used to distinguish between ultrarapid and poor metabolizers. All but one of the nonresponders in this study had lower ratios than the responders. Three

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patients (9%) had homozygous defective CYP2D6 alleles and did not readily metabolize venlafaxine to O-desmethylvenlafaxine, pointing to poor metab. In these patients, N-desmethylation was increased. Two out of four patients detected by the ratio as potentially ultrarapid metabolizers were shown to have multiple copies of a functional CYP2D6 gene.

IT 93413-62-8, O-Desmethylvenlafaxine 149289-30-5,  
N-Desmethylvenlafaxine  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
(Biological study); PROC (Process)  
(serum concns. of venlafaxine and metabolites in humans and CYP2D6  
genotype)

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2002 ACS  
AN 1998:375348 CAPLUS  
DN 129:144527  
TI Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk  
AU Ilett, K. F.; Hackett, L. P.; Dusci, L. J.; Roberts, M. J.; Kristensen, J. H.; Paech, M.; Groves, A.; Yapp, P.  
CS Department of Pharmacology, University of Western Australia, Nedlands, 6907, Australia  
SO British Journal of Clinical Pharmacology (1998), 45(5), 459-462  
CODEN: BCPHBM; ISSN: 0306-5251  
PB Blackwell Science Ltd.  
DT Journal  
LA English  
AB To characterize the transfer of venlafaxine (V) and its O-desmethyl metabolite (ODV) into human milk by measuring milk/plasma (M/P) ratio, and to est. the likely dose received by a breast-fed infant. Milk and plasma samples were collected from three lactating women who were taking venlafaxine for depression, and were at steady-state. In two of the patients, venous blood and milk samples were collected 0, 1, 2, 3, 4, 6, 8 and 12 h post dose, while in the third patient a single pair of blood and milk samples was obtained 0.83 h post dose. A plasma sample was obtained from each of their infants. V and ODV were measured in plasma and milk by high performance liq. chromatog. M/P was calcd. and infant dose estd. as drug concn. in milk .times. a milk intake of 0.15 l kg<sup>-1</sup> day<sup>-1</sup>, relative to the wt.-adjusted maternal dose. Mean M/P for V was 4.1 (range 2.8-4.8) and 3.1 for ODV (range 2.8-3.8). The mean total infant dose (as V equiv.) was 7.6% (range 4.7-9.2%) of the maternal wt.-adjusted dose, with approx. equal amts. of V (3.5%) and ODV (4.1%) in the dose. ODV (median 100 .mu.g l<sup>-1</sup>) was detected in the plasma of all three infants. The infants were healthy and showed no acute adverse effects. These preliminary data show that the total dose of V and ODV ingested by breast-fed infants can be as high as 9.2% of maternal intake. Moreover there were measurable concns. of ODV in the infants' plasma. We recommend that exposed infants should be obsd. closely.  
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IT 93413-62-8, O-Desmethylvenlafaxine

RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)

(distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk)

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2002 ACS

AN 1998:340269 CAPLUS

DN 129:76011

TI The influence of cimetidine on the disposition kinetics of the antidepressant venlafaxine

AU Troy, Steven M.; Rudolph, Richard; Mayersohn, Michael; Chiang, Soong T.

CS Wyeth-Ayerst Research, Philadelphia, PA, 19101, USA

SO Journal of Clinical Pharmacology (1998), 38(5), 467-474

CODEN: JCPCBR; ISSN: 0091-2700

PB Lippincott-Raven Publishers

DT Journal

LA English

AB The influence of cimetidine on the disposition pharmacokinetics of the antidepressant drug venlafaxine and its active metabolite, O-demethylvenlafaxine, was examd. in healthy young men and women. The steady-state pharmacokinetic profiles of venlafaxine and O-demethylvenlafaxine were evaluated during a 24-h period after 5 days of treatment with venlafaxine (50 mg 3 times a day) and during a 2nd 24-h period after 5 days of combination treatment with venlafaxine (50 mg 3 times a day) and cimetidine (800 mg once a day). The apparent oral clearance of venlafaxine decreased and the av. steady-state plasma concn. of venlafaxine increased in the presence of cimetidine, but there were no changes in the corresponding concns. of the active metabolite. However, O-demethylvenlafaxine has a pharmacol. activity that is approx. equipotent to that of venlafaxine, and the sum of plasma venlafaxine plus O-demethylvenlafaxine concns. was increased by an av. of only 13%. Therefore, the effect of cimetidine coadministration is not expected to result in clin. important alterations in the response to venlafaxine in patients with depression. This may not be true, however, for patients with compromised hepatic metabolic function.

AB The influence of cimetidine on the disposition pharmacokinetics of the antidepressant drug venlafaxine and its active metabolite, O-demethylvenlafaxine, was examd. in healthy young men and women. The steady-state pharmacokinetic profiles of venlafaxine and O-demethylvenlafaxine were evaluated during a 24-h period after 5 days of treatment with venlafaxine (50 mg 3 times a day) and during a 2nd 24-h period after 5 days of combination treatment with venlafaxine (50 mg 3 times a day) and cimetidine (800 mg once a day). The apparent oral clearance of venlafaxine decreased and the av. steady-state plasma concn. of venlafaxine increased in the presence of cimetidine, but there were no changes in the corresponding concns. of the active metabolite. However, O-demethylvenlafaxine has a pharmacol. activity that is approx. equipotent to that of venlafaxine, and the sum of plasma venlafaxine plus O-demethylvenlafaxine concns. was increased by an av. of only 13%. Therefore, the effect of cimetidine coadministration is not expected to result in clin. important alterations in the response to venlafaxine in patients with depression. This may not be true, however, for patients with compromised hepatic metabolic function.

IT 93413-62-8, O-Desmethylvenlafaxine

CAPLUS ONLINE PRINTOUT

RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)  
(cimetidine effect on the disposition kinetics of venlafaxine in humans, with formation of)

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2002 ACS  
AN 1997:681434 CAPLUS  
DN 127:355027  
TI Application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects  
AU Taft, David R.; Iyer, Ganesh R.; Behar, Leon; DiGregorio, Robert V.  
CS Division of Pharmaceutics and Industrial Pharmacy, Long Island University, Brooklyn, NY, 11201, USA  
SO Drug Metabolism and Disposition (1997), 25(10), 1215-1218  
CODEN: DMDSAI; ISSN: 0090-9556  
PB Williams & Wilkins  
DT Journal  
LA English  
AB Venlafaxine (VEN), a drug used in the treatment of depression, undergoes significant first-pass metab. after oral dosing to O-desmethylvenlafaxine (ODV), a metabolite with comparable therapeutic activity to that of parent drug. The pharmacokinetic disposition of VEN was characterized using a "first-pass" model that incorporates a presystemic compartment (liver) to account for the first-pass metab. of VEN to ODV. A series of differential equations were simultaneously fitted to plasma concns. of parent and metabolite. A good fit of the model to obsd. data was demonstrated, generating ests. for the following parameters: ka (1.31 h<sup>-1</sup>), VVEN (252 L), CLint (65.8 L/h), RL (liver:plasma partition coeff., 29.6), VODV (181 L), and CLODV (23.5 L/h). Parameter ests. correlated closely with those obtained through noncompartmental methods. These results indicate that the time-course disposition of a compd. undergoing first-pass hepatic metab. after oral dosing can be successfully modeled.  
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IT 93413-62-8, O-Desmethylvenlafaxine  
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)  
(application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects)  
L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2002 ACS  
AN 1996:444791 CAPLUS  
DN 125:107239  
TI Two fatal cases of venlafaxine poisoning

CAPLUS ONLINE PRINTOUT

AU Parsons, Ann T.; Anthony, Robert M.; Meeker, James E.  
CS Laboratory Forensic Services, Sacramento, CA, 95820, USA  
SO J. Anal. Toxicol. (1996), 20(4), 266-268  
CODEN: JATOD3; ISSN: 0146-4760  
DT Journal  
LA English  
AB Venlafaxine is a phenethylamine deriv. that has recently been approved for use in the treatment of depression. It is chem. unrelated to tricyclic, tetracyclic, or other available antidepressant agents. Anticholinergic, hypotensive, hypertensive, and cardiotoxic side effects are rare. Two fatal cases encountered at sep. labs. are discussed, both involving high levels of venlafaxine. The concns. of the drug in peripheral blood, heart blood, urine, vitreous humor, and liver are reported. Descriptions of extn. and gas chromatog. methods for confirmation and quantitation are included.  
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IT 93413-62-8, O-Desmethylvenlafaxine 93413-69-5, Venlafaxine  
RL: ANT (Analyte); ANST (Analytical study)  
(tissue distribution of venlafaxine and its metabolite in humans after fatal poisoning)

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CAPLUS ONLINE PRINTOUT

AN 1997:681434 CAPLUS  
DN 127:355027  
TI Application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects  
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IT 93413-62-8, O-Desmethylvenlafaxine  
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)  
(application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects)